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The Cancer Stem Cell Paradigm and Mathematical Modelling - A Brief Summary

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The cancer stem cell (CSC) idea has been gaining lots of traction and popularity in recent times as the challenges to finding solutions to the problems posed by cancer persist. It is believed that most tumours are heterogeneous and many cancers contain small populations of highly tumorigenic and intrinsically drug resistant cancer stem cells (CSCs). Like normal stem cells, CSCs have the ability to self-renew and differentiate into other tumour cell types. They are believed to be a source for drug resistance, tumour recurrence, and metastasis. CSCs often over-express drug efflux transporters, spend most of their time in the non-dividing G0 cell cycle state, and are therefore, capable of escaping the effects of treatments that include conventional chemo- and radio-therapies (1–5). CSCs have been said to arise either from normal stem cells or from normal progenitor cells (4) and experiments show that they can be generated from normal stem cells. They are also adjudged to be similar to normal somatic stem cells that are pluripotent stem cells found in a number of organs and are responsible for tissue regeneration and repair. The best-investigated and most comparable somatic and cancer stem cells are hematopoietic stem cells (HSCs) and leukemic stem cells (LSCs) (2) and studies of tumours such as leukaemia and lymphoma, for example, suggest that the CSCs can be derived from either HSCs, or from progenitor cells that have gained the ability to self-renew (4). In any case, it must be pointed out that irrespective of how CSCs arise, the main thrust of the CSC concept is that the properties of functional heterogeneity exist within tumours with the presence of a distinct rare population of cells, no matter how small, that drives tumorigenesis. This distinct population that has the properties of quiescence, self-renewal, and proliferation may be responsible for supporting resistance to different forms of therapy and also for causing relapses. Gaining deeper insights into the development of stem cells in general and CSCs in particular with the aim of interfering with the emerging CSC population for the purpose of bringing about its eradication poses challenges to biomedical research and engenders approaches from various viewpoints including by mathematical modelling. It is within this setting that our recent article (6) notably adds to needed contributions in a space that remains largely unoccupied with regards to the use of necessary mathematical tools for understanding certain processes that cannot be deciphered from biomedical experiments.

Gaining deeper insights into the development of stem cells through mathematical modelling

From what we just said above, we note that CSC-driven mathematical modelling has not yet risen to the level of an extensive research activity at this time because of the recently emerging nature of the CSC paradigm itself that now demands active biomedical research aimed at establishing and building on the required biological information needed about CSCs. Nonetheless, the few CSC-driven mathematical models that have appeared hold promise for witnessing a future that is filled with the appropriate interfacing of the various scientific disciplines that include mathematics in facing the problems brought on by cancer and its various formations. Most of the CSC-driven mathematical models (7, 8) have utilized ordinary differential equation

(ODE) description approaches because such approaches are more suited to capturing the hierarchically structured nature of CSC development that is amenable to compartmentalization. In general, the models quantify dynamics exhibited by normal stem, early progenitor, late progenitor, and mature cells, and their abnormal counterparts, respectively, to arrive at conclusions regarding mutations and overall cancer risk. In recent work (6), we also used an ODE formulation to study a nonlinear model that was based on normal and abnormal cells, including CSC, behaviour in the bone marrow (BM) and peripheral blood (PB).

Using ordinary differential equation description approaches

With the CSC idea having gained a good level of traction as is exemplified by the works from various viewpoints in the literature (1–5, 7, 8), we (6), set out to bring our earlier activities to the current state of thinking that involves CSCs by updating models proposed and studied(9). Moving specifically from investigation of normal state dynamics in the BM and PB (9), dynamics in these environments in the disease state were considered by merging the views propounded by Clarkson (10) that normal and abnormal cells exist side-by-side in the cancerous state, with the CSC ideas. These considerations in addition to more relevant biomedical information led to a number of assumptions that in turn led to the nonlinear model system studied (6).

Among other things, analysis and simulations of the model produced the following notable conclusions:

1. Achievement of malignant dominance of the entire bone marrow - peripheral blood architecture occurs through the evolution towards steady states in which any semblance of cell normality, portrayed through the presence of normal cells, is ultimately rendered non-existent.
2. The three main factors that guarantee and propel the persistence of malignancy may be mutation, malignant cell replication, and release of malignant cells from the marrow into the peripheral blood.
3. Evolution of three steady states: the trivial steady state in which no normal or malignant cells are ultimately present; the axial equilibrium that shows complete dominance by the malignant populations in the BM and PB; and the steady state of coexistence, the interior equilibrium. The most persistent steady state then turns out to be the axial equilibrium.
4. Once the hematopoietic system evolves towards a malignant state, such a state becomes irreversible in the absence of treatment and the effort needed to completely disrupt this state may entail the total eradication of all cells including the normal ones. This model prediction suggests that a great deal of attention needs to be focused on prevention of malignancy. In the case where malignancy is detected. Furthermore, very robust treatment strategies that aim at driving the malignant mass to the barest minimum while protecting normal tissues may have to be devised in containing it.

We are continuing our research on CSCs with the hope of using our models to capture more intricate characteristics of CSC behaviour.

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